REMARKS

Claim 1 has been amended. Claims 8 and 41 have been canceled. Support for the amendments in Claim 1 can be found in paragraphs **[0018]**, **[0037]**, **[0040]**, **[0041]** of the Substitute Specification as filed on April 18, 2003; in the Abstract filed August 7, 2001; in Claim 41 as filed on April 28, 2003, an in Claim 8 as filed on March 23, 2001. Therefore, no new matter has been introduced herewith. The following addresses the substance of the Office Action.

Claim rejections under 35 U.S.C. §112

The Examiner has rejected Claims 1, 2, 4, 8-10, 12-23, 38 and 40-45 under 35 U.S.C. §112, second paragraph as being allegedly indefinite. More specifically, the independent Claim 1 was asserted to be indefinite in recitation of "nucleic acid characteristic" was asserted to not be defined in the Specification; and in recitation of "said nucleotide sequence", "said homologous nucleotide sequences", and "said amplified or copied nucleotide sequence" for allegedly lacking antecedent basis.

The Applicants have amended the independent Claim 1 to now recite: "nucleotide sequence specific", supported in paragraph **[0018]** of the Substitute specification; "said specific nucleotide sequence", "homologous nucleotide sequences", and "said target nucleotide sequence" all having proper antecedent basis in claim 1. Withdrawal of the rejection 35 U.S.C. §112, second paragraph is respectfully requested.

Claim rejections under 35 U.S.C. §103

The Examiner has rejected Claims 1, 2, 4, 8-10, 12-23, 38 and 40-45 under 35 U.S.C. §103(a) as being allegedly unpatentable over Brown *et al.* (USP 5,807,522) in view of Vannuffel *et al.* (WO 99/16780), and further in view of Bamdad *et al.* (USP 6,541,617). More specifically, the Examiner alleges that in view of the techings of Vannuffel *et al.* it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Brown *et al.* so as to have included the consensus sequences (i.e. primers and probes) specific for the *fem*A sequence of Staphylococcal species of Vannuffel *et al.*, in order to achieve the benefit of providing an effective means of detecting specific species of the Staphylococci genus for use in diagnosing staphylococcal infections, for example. The Examiner also alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to

have modified the method of Brown *et al.* so as to have used a spacer of at least 6.8 nm, in order to achieve the benefits stated by Bamdad *et al.* of increasing the kinetics of hybridization, thus providing a more efficient means of hybridization/detection. The Applicant respectfully disagrees.

To establish a *prima facie* case of obviousness, the PTO must cite one or more references that provide some suggestion or motivation to modify the references to achieve the claimed invention, provide a reasonable expectation of success to achieve the claimed invention, and finally, the cited art must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). "We do not 'pick and choose among the individual elements of assorted prior art references to recreate the claimed invention,' but rather, we look for 'some teaching or suggestion in the references to support their use in the particular claimed combination.'" *Symbol Technologies, Inc. v. Opticon, Inc.* 935 F.2d 1569 (Fed. Cir. 1991). Here, the cited art either taken alone or in combination, fails to provide the required factors.

In the presently claimed invention, the capture nucleotide sequences are covalently bound to an array. Brown teaches capture probes non-covalently immobilized on polylysine coated on the surface of glass slides, therefore it in fact teaches away from the present invention as claimed in currently amended Claim 1. In addition, in the method of Brown, the capture probes are immobilized on polylysine coated on the surface of glass slides. In such methods, there is no control of which portion of the probe is available for hybridization. Such methods are not desirable where one aims to discriminate between closely related sequences, since if the specific portion of the probe is bound to the support it will be unavailable for specific hybridization.

Moreover the electrostatic binding method of Brown is not desirable for binding short probes of less than 50 bases (page 4, lines 20-21) because the retention is very weak and is not compatible with the use of stringent condition as required by the hybridization on a microarray designed to discriminate homologous sequences which can differ by one or a few bases. In contrast, the presently pending claims recite that the probes are about 15 to about 40 bases in length.

Finally, the methods of Brown are not intended for specifically identifying or quantitating an organism using a sequence having at least 60% homology with the sequences of other organisms.

Thus, there is no teaching or suggestion in Brown of covalently binding the probes to the array nor are the methods of Brown suitable for use with probes of the lengths recited in the presently pending claims. In addition, Brown provides no motivation to combine arrays comprising covalently bound probes, probes of the lengths recited in the claims, and primer pairs capable of amplifying at least two of 4 homologous sequences in methods for detecting specific nucleotide sequences having a homology level higher than 60% with sequences from other organisms.

In the presently claimed invention, the nucleotide sequences are covalently bound to an array and are about 15 to about 40 bases in length. The nylon membranes of Vanuffel have probes non-covalently bound threreto, and thus, like the membranes of Brown, are not desirable for use in discriminating between homologous sequences because the portion of the probe which is available for hybridization is not controlled. Furthermore, although Vanuffel mentions nucleic acids having a length between 15 and 350 base pairs, the hybridization probes utilized in the examples of Vanuffel are longer than those recited in the presently pending claims. Particularly, the lengths of the specific double-stranded probes in the working examples of Vannuffel *et al.* (see Example 4) are 286 and 220 base pairs long. Probes of such lengths would be ineffective in discriminating between sequences having greater that 60% homology, as recited in the presently pending claims, because there would be some portion of the long probe which would bind to all of the related sequences. There is no discussion of advantages of shorter capture probes in Vannuffel *et al.* Furthermore, there is no suggestion in Vanuffel to combine arrays comprising covalently bound probes, probes of the lengths recited in the claims, and primer pairs capable of amplifying at least two of 4 homologous sequences in methods for detecting specific nucleotide sequences having a homology level higher than 60% with sequences from other organisms.

Bamdad *et al.* teaches the use of colloid particles comprising binding ligands and electron transfer moieties (ETM) for covalent binding of target analyte to an electrode surface. Bamdad further teaches that for efficient hybridization of nucleic acids on a surface, the hybridization should occur at a distance from the surface. However, this document also teaches that a spacer between 15 and 60 Å and up to 500 Å long for positioning a nucleic acid on a surface is particularly important for long double-stranded oligonucleotides of 200 to 300 basepairs. Therefore, based on the teaching of Bamdad *et al.* it would not have been obvious for an ordinary

skilled person to use a spacer of 6.8 nm long for positioning of short 15-40 bases single-stranded DNA sequences. Furthermore, there is no suggestion in Bamdad to to combine arrays comprising covalently bound probes, probes of the lengths recited in the claims, and primer pairs capable of amplifying at least two of 4 homologous sequences in methods for detecting specific nucleotide sequences having a homology level higher than 60% with sequences from other organismsutilize covalently bound probes or probes of the lengths recited in the claims.

Therefore, the combination of Brown *et al.*, Vannuffel *et al.* and Bamdad *et al.* does not render the claimed invention obvious. Accordingly, withdrawal of the rejection of Claims 1, 2, 4, 8-10, 12-23, 38 and 40-45 under 35 U.S.C. §103(a) is respectfully requested.

The Examiner has rejected Claim 18 under 35 U.S.C. §103(a) as being allegedly unpatentable over Brown *et al.* (USP 5,807,522) in view of Vannuffel *et al.* (WO 99/16780), in view of Bamdad *et al.* (USP 6,541,617) and further in view of Boon *et al.* (USP 6,488,932).

More specifically, the Examiner alleges, that is would have been obvious to a person with ordinary skill in the art at the time the invention was made to have modified the method of Brown *et al.*, Vannuffel *et al.*, and Bamdad *et al.* by including the steps of detecting a sequence belonging to the MAGE family, in order to have achieved the benefit of providing an effective means of diagnosing tumor.

Boon's disclosure of the use of the MAGE family to diagnose tumors does not provide motivation to to combine arrays comprising covalently bound probes, probes of the lengths recited in the claims, and primer pairs capable of amplifying at least two of 4 homologous sequences in methods for detecting specific nucleotide sequences having a homology level higher than 60% with sequences from other organisms. Thus, Boon *et al.* fails to correct the failure of Brown *et al.*, Vannuffel *et al.* and Bamdad *et al.* to render the claimed invention obvious for the reasons addressed above. Therefore, dependent Claim 18 is also non-obvious.

The Examiner has rejected Claim 9 under 35 U.S.C. §103(a) as being allegedly unpatentable over Brown *et al.* (USP 5,807,522) in view of Vannuffel *et al.* (WO 99/16780), in view of Bamdad *et al.* (USP 6,541,617) and further in view of Apple *et al.* (USP 5,451,512).

More specifically, the Examiner alleges, that is would have been obvious to a person with an ordinary skill in the art at the time the invention was made to have modified the method of Brown *et al.*, Vannuffel *et al.*, and Bamdad *et al.* by including the steps of detecting a sequence

belonging to the HLA-A family, in order to achieve the benefit of providing an effective means of minimizing the risk of implantation rejection.

Apple's disclosure of the benefits of detecting members of the HLA-A family does not provide motivation to to combine arrays comprising covalently bound probes, probes of the lengths recited in the claims, and primer pairs capable of amplifying at least two of 4 homologous sequences in methods for detecting specific nucleotide sequences having a homology level higher than 60% with sequences from other organisms. Thus, Apple fails to correct the failure of Brown *et al.*, Vannuffel *et al.* and Bamdad *et al.* to render the claimed invention obvious for the reasons addressed above. Therefore, dependent Claim 9 is also non-obvious.

The Examiner has rejected Claims 20 and 22 under 35 U.S.C. §103(a) as being allegedly unpatentable over Brown *et al.* (USP 5,807,522) in view of Vannuffel *et al.* (WO 99/16780), in view of Bamdad *et al.* (USP 6,541,617) and further in view of Klein *et al.* (USP 6,255,059).

More specifically, the Examiner alleges, that is would have been obvious to a person with an ordinary skill in the art at the time the invention was made to have modified the method of Brown *et al.*, Vannuffel *et al.*, and Bamdad *et al.* by including the steps from Klein *et al.* of detecting a sequence belonging to the dopamine or histamine receptors coupled to the G genes family.

Klein's disclosure of the benefits of detecting dopamine or histamine receptors coupled to the G gene family does not provide motivation to to combine arrays comprising covalently bound probes, probes of the lengths recited in the claims, and primer pairs capable of amplifying at least two of 4 homologous sequences in methods for detecting specific nucleotide sequences having a homology level higher than 60% with sequences from other organisms. Thus, Klein fails to correct the failure of Brown *et al.*, Vannuffel *et al.* and Bamdad *et al.* to render the claimed invention obvious for the reasons addressed above. Therefore, dependent Claims 20 and 22 are also non-obvious.

The Examiner has rejected Claim 21 under 35 U.S.C. §103(a) as being allegedly unpatentable over Brown *et al.* (USP 5,807,522) in view of Vannuffel *et al.* (WO 99/16780), in view of Bamdad *et al.* (USP 6,541,617) and further in view of Murphy *et al.* (WO 94/05695).

More specifically, the Examiner alleges, that is would have been obvious to a person with an ordinary skill in the art at the time the invention was made to have modified the method of Brown *et al.*, Vannuffel *et al.*, and Bamdad *et al.* by including the steps from Murphy *et al.* of detecting a sequence belonging to the choline receptors coupled to the G genes family.

Murphy's disclosure of the benefits of detecting choline receptors coupled to the G gene family does not provide motivation to to combine arrays comprising covalently bound probes, probes of the lengths recited in the claims, and primer pairs capable of amplifying at least two of 4 homologous sequences in methods for detecting specific nucleotide sequences having a homology level higher than 60% with sequences from other organisms. Thus, Murphy fails to correct the failure of Brown *et al.*, Vannuffel *et al.* and Bamdad *et al.* to render the claimed invention obvious for the reasons addressed above. Therefore, dependent Claim 21 is also non-obvious.

For the foregoing reasons, it is respectfully submitted that the rejections set forth in the outstanding Office Action are inapplicable to the present claims. Accordingly, Applicants request withdrawal of all the rejections under 35 U.S.C. §103(a) and the expeditious allowance of the pending claims.

CONCLUSION

In view of the foregoing, Applicants respectfully submit the present application is fully in condition for allowance. If any issues remain that may be addressed by a phone conversation, the Examiner is invited to contact the undersigned at the phone number listed below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: Feb. 10, 2004

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